REMARKS

Claims 40-44, 48-62 and 64 are pending in this application. Claims 54-59 and 64 are withdrawn from consideration, as being directed to a non-elected invention. Claims 40-44, 48, and 51 stand rejected. Claims 49, 50, 52, 53, and 60-62 are objected to. Claim 40 is amended herein. Support for this amendment is provided at page 21, lines 30-37, page 24, lines 28-34, and page 25, lines 11-14 of the instant specification. Thus, no new matter is added.

Objections

Claims 49, 50, 52, 53, and 60-62 are objected to. These claims are objected to on the Office Action Summary; however, the Examiner does not indicate within the Office Action any grounds for these objections. These claims are, therefore, not amended herein.

Rejection Under 35 U.S.C. § 103

Claims 40-44, 50, and 51 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Adair, *et al.* (WO 91/09967, published 7/11/91) in view of Vijh-Warrier, *et al.* (*Molecular Immunology* 32:1081-1092, 1995) and Queen, *et al.* (U.S. Patent No. 5,693,762). In particular, the Examiner alleges that, "Adair, *et al.* teach methods of CDR grafting comprising acceptor framework and donor antigen binding regions of rodent antibodies (see abstract). Adair, *et al.* also teach non-CDR residues which contribute to antigen binding and CDR contacting residues (see page 20-23) and replacing residues that influence CDR or antigen binding and those that are in a salt bridge (see page 21) and constant regions from humans (see page 12)."

Furthermore, the Examiner alleges that, "Vijh-Warrier, *et al.* teach the nucleotide and amino acid sequence of the variable region of a *Pan troglodyte* antibody (see abstract). Vijh-Warrier also teach several human germline variable region genes (see Figure 3, 4, and 5, and

Table 1) and that chimpanzee mAbs are no more likely to elicit deleterious anti-immunoglobulin responses in humans than human mAbs (see page 1089)."

Finally, the Examiner alleges that Queen, *et al.* teach "CDR grafting of donor CDRs onto human or humanized frameworks and replacing frameworks of the acceptor when within 3Å or residues influencing the van der Waal forces of a CDR residue or interacting in hydrophobic interactions with a CDR residues (see column 14, lines 26-50)." The Examiner further alleges that one of ordinary skill in the art would have been motivated to and have had a reasonable expectation of successfully producing the claimed invention because Vijh-Warrier, *et al.* suggest that chimpanzee mAbs are not more likely to elicit deleterious anti-immunoglobulin responses in humans than are human mAbs.

Applicant respectfully submits that for a proper obviousness rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing *prima facie* with evidence or reasons that, *inter alia*, at the time of the invention, (1) the prior art of record would have suggested or motivated one of ordinary skill in the art to carry out the combination and modification of the prior art as suggested by the Examiner to arrive at the claimed invention, and (2) "the prior art would also have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success. Both the suggestion [or motivation] and the reasonable expectation of success must be founded in the prior art, not in the appellants' disclosure." *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991) (citations omitted).

Applicant traverses this rejection and respectfully submits that neither Adair, *et al.*, Vijh-Warrier, *et al.* nor Queen, *et al.* teach or suggest the instantly claimed antibodies. None of the cited references, either independently or in combination, teach or suggest an antibody comprising CDRs from rodent and framework from Old World Ape combined with at least one human constant region as Applicant instantly claims. More importantly, none of the

cited references suggest this combination, resulting in an antibody having a binding avidity within about three-fold of the binding avidity of donor antibody, as amended claim 40 and dependent claims 41-44, 48-53 and 60-62 now recite.

Adair, *et al.* disclose antibodies containing non-human CDRs grafted into a human framework. Adair, *et al.* do not teach or suggest that the framework region of the acceptor antibody be from Old World Ape. While Adair, *et al.* indicate acceptor framework residues that may effect antigen binding, the effect of replacing these residues is based on framework from human only. Adair, *et al.* make no suggestion that making replacements in a non-human framework would have the same effect as replacing residues in a human framework.

Vijh-Warrier, *et al.* merely disclose a comparison of variable regions of a single chimpanzee monolconal antibody, raised against HIV, with variable regions of antibodies from similar human germlines. Moreover, Vijh-Warrier, *et al.* present sequence homology between chimpanzee nucleic acid and amino acid sequences from the variable regions of C108G with "the most homologous human germline variable regions," *see* Table 1, page 1088. The data in this table of Vijh-Warrier, *et al.* demonstrate that none of the framework regions have greater than 97% sequence homology, and most have less than 95% sequence homology. Furthermore, a comparison of the CDR regions in Vijh-Warrier, *et al.* of selected chimpanzee and human antibodies shows a much lower sequence homology, on the order of about 60-73%.

Applicant respectfully submits that these data presented by Vijh-Warrier, *et al.* do not provide the skilled artisan with a reasonable expectation of success in producing an antibody with a binding avidity similar to rodent and comprising CDR from rodent and framework regions from chimpanzee, even when taken in combination with Adair, *et al.* and Queen, *et al.* First Vijh-Warrier, *et al.* only suggest that using antibodies from chimpanzee will reduce

immunogenicity in humans. Vijh-Warrier, *et al.* do not mention antigen recognition of an antibody comprising CDRs from rodent and framework from chimpanzee. Thus, Vijh-Warrier, *et al.* provide no suggestion that replacements in the acceptor framework will affect antigen binding.

Second, Applicant respectfully disagrees with Vijh-Warrier, *et al.*'s assumption that homologous framework regions between species will necessarily result in a reduction in immunogenicity during passive immunization. It is well known in the art that anti-idiotypic antibodies are generated when an antibody from a first species is administered to a second. For instance, human-anti-mouse antibodies (HAMA) arise when mouse antibody is administered to a human. It is also known that, anti-idiotypic antibodies can involve amino acid residues from both the hypervariable region and framework region. *See* Greenspan and Bona. *FASEB J* (1993) Mar;7(5):437-444 (abstract). *See* attached IDS form 1449 and abstract provided herein. In fact, it is understood in the art that humans may show an immunoresponse to their own antibodies, human anti-human response (HAHA). *See* Kuus-Reichel, *et al., Clinical and Diagnostic Laboratory Immunology*, July 1994:365-372. *See* attached IDS form 1449 and article provided herein. Applicant respectfully submits that, even if a greater homology exists for framework regions than hypervariable regions between chimpanzee and human antibodies to the same antigen, the skilled artisan would not necessarily expect homologous framework regions to reduce immunogenicity. Vijh-Warrier, *et al.* disclose that the CDR regions of antibodies from chimpanzee and human are no more than 73% homologous, at least in the case of antibodies raised to HIV. Thus, the skilled artisan might expect a human, passively immunized with a chimpanzee antibody, to develop anti-idiotypic antibodies.

Third, Vijh-Warrier, *et al.* indicate that even in the most homologous chimpanzee and human antibodies, amino acid sequences of the framework regions are not identical between species. Both Adair, *et al.* and Queen, *et al.*, suggest that a single or small number of amino acid changes in the framework region of an antibody comprising CDRs from rodent and framework from human may effect antigen binding. Thus, if a framework region is not 100% homologous to human, then a skilled artisan cannot reasonably expect that making amino acid changes in an Old World Ape framework will successfully have the same effect as making the same type substitutions in a human framework.

More importantly, Vijh-Warrier, *et al.* does not present any data relating the binding avidity of a fused antibody. Vijh-Warrier, *et al.* merely suggests using antibodies raised in chimpanzees for passive immunotherapy to reduce immunogenicity in humans. Neither Queen, *et al.* nor Vijh-Warrier, *et al.,* either separately or in combination, teach or suggest that framework sequences from Old World can be combined with rodent CDRs. Thus, Applicant respectfully submits that the skilled artisan would not expect success in making donor residue substitutions in an acceptor framework from Old World Ape based on the teachings of Adair, *et al.* Queen, *et al.* and Vijh-Warrier, *et al.*

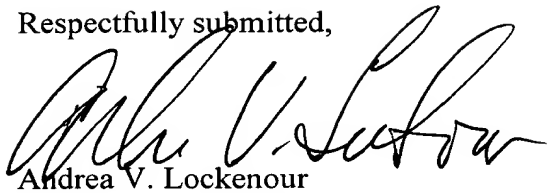
In summary, Applicant respectfully submits that the Examiner impermissibly uses hindsight reconstruction with Adair, *et al.*, Vijh-Warrier, *et al.* and Queen, *et al.* to make this *prima facie* obviousness rejection. He has met neither prong of his burden required by *In re Vaeck, supra* for the following reasons. Aidar, *et al.* disclose a combination of rodent CDRs with human framework, with selected substitution in the acceptor framework to improve antigen binding. Vijh-Warrier, *et al.* present data for a selected antibody raised against HIV in chimpanzee. They do not disclose an antibody having CDRs from a rodent and a framework from Old World Ape. In addition, Vijh-Warrier, *et al.* do not disclose altering a

primate framework region to improve antigen binding. They merely suggest that homologous framework sequences could reduce immunogenicity in passive immunization. Applicant respectfully submits that homology in the framework region may not be an accurate indicator of an antibody that will reduced immunogencity. Immunoresponse may also arise against the CDR region of an antibody. Finally, as demonstrated by Queen, *et al.* a single or small number of changes in amino acid residues of a human framework region can alter antibody binding affinity, *see* for instances column 13, lines 55-63 of Queen, *et al.* Because, the framework regions of Old World Ape antibodies differ from humans the same changes do not have predictably the same effect. It is only after Applicant has made the instantly claimed invention, that he has revealed an antibody having CDRs from rodent and framework from Old World Ape, which maintains binding avidity as compared with an antigen specific donor antibody.

Applicant respectfully submits that in view of the forgoing amendments and remarks, he has overcome the Examiner's rejection of claims 40-44, 48 and 51 under 35 U.S.C. § 103. Reconsideration and withdrawal of these rejections is respectfully requested.

Applicant reserves the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the cancelled claims, the claims as originally filed, and any other claims supported by the specification. Applicant thanks the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited. If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicant's undersigned attorney.

Respectfully submitted,



Andrea V. Lockenour
Attorney for Applicant
Registration No. 51,962

GLAXOSMITHKLINE
Corporate Intellectual Property-UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone: (610) 270-7568
Facsimile: (610) 270-5090
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